SYSTEMS, METHODS, AND KITS FOR DIAGNOSTICS AND TREATMENT OF VIRAL RESPIRATORY INFECTION

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a divisional application to U.S. Utility application Ser. No. 16/946,875, which claims the benefit of U.S. Provisional Application No. 63/041,426, titled Methods and Compositions for the Treatment of Viral Respiratory Infection, filed on Jun. 19, 2020, and is a continuation in part application to U.S. Utility application Ser. No. 15/929,788, titled Systems, Methods, and Kits for Diagnostics and Treatment of Viral Respiratory Infection, filed on May 21, 2020, which is related to and claims the benefit of U.S. Provisional Application No. 63/001,629, titled Systems, Methods and Kits for Diagnostics and Treatment of SARS-CoV-2, filed on Mar. 30, 2020, U.S. Provisional Application No. 63/004,171, titled Systems, Methods and Kits for Diagnostics and Treatment of Viral Respiratory Infection, filed on Apr. 2, 2020, U.S. Provisional Application No. 63/004,398, titled Systems, Methods and Kits for Diagnostics and Treatment of Viral Respiratory Infection, filed on Apr. 2, 2020, U.S. Provisional Application No. 62/704,126, titled Systems, Methods and Kits for Diagnostics and Treatment of Viral Respiratory Infection, filed on Apr. 22, 2020, U.S. Provisional Application No. 62/704,416, titled Systems, Methods and Kits for Diagnostics and Treatment of Viral Respiratory Infection, filed on May 8, 2020, U.S. Provisional Application No. 62/704,531, titled Systems, Methods and Kits for Diagnostics and Treatment of Viral Respiratory Infection, filed on May 14, 2020, the entire contents of each being incorporated herein by reference.

FIELD

[0002] The present invention relates to systems, methods, compositions and kits for treating, preventing, and diagnosing viral infection using a combination of thyroid hormone pathways and androgen mediated pathway. The present invention relates to methods and kits for predicting viral respiratory disease severity. Additionally, the present invention relates to methods and kits for guiding treatment of viral respiratory disease by testing for polymorphisms in the androgen receptor gene or genes under regulatory control of the androgen receptor. Similarly, the following invention relates to systems and methods for treatment of viral respiratory diseases with various anti-androgens used in combination with thyroid inhibitors including, but not limited to, androgen receptor antagonists, androgen synthesis inhibitors, or antigonadotropins used in combination with TGF-β inhibitors, thyroid hormone receptor inhibitors, thyroid inhibitors, or furin protease inhibitors. Additionally, the present systems, methods, and kits are useful for treating, preventing, and diagnosing coronavirus, e.g., SARS-CoV-2 (COVID-19).

BACKGROUND

[0003] In late 2019, a novel coronavirus, subsequently named SARS-CoV-2 (COVID-19), was first reported in Hubei province in China. Since it was first reported, a worldwide pandemic has ensued affecting more than 450,000 individuals as of March 2020. In the midst of the pandemic, epidemiological reports unveiled a disproportionate low rate of severe cases among adult females compared to adult males, 42% and 58%, respectively. Similarly, the rate of severe cases among pre-pubescent children was exceptionally low at 0.6% (See Guan W J, Ni Z Y, Hu Y, Liang W H, Ou C Q, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020). An explanation for the skewed prevalence of severe COVID-19 infection in adult males has yet to be elucidated.

[0004] In newborns, it has long been recognized that male infants are more susceptible to respiratory distress syndrome (See Torday J S, Nielsen H C, Fend Mde M, Avery M E. Sex differences in fetal lung maturation. Am Rev Respir Dis. 1981; 123(2): 205-208) and less likely to respond to prenatal glucocorticoid therapy to protect against respiratory distress. Respiratory distress is intimately tied to the production of pulmonary surfactant, e.g., pulmonary surfactant proteins have been demonstrated to protect against influenza A (See Hartshorn K L, Crouch E C, White M R, Eggleton P, Tauber A I, Chang D, Sastry K. Evidence for a Protective Role of Pulmonary Surfactant Protein D (SP-D) Against Influenza A Viruses. J Clin Invest. 1994; 94 (1): 311-319). In animal studies, it was demonstrated that a sexual dimorphism in fetal pulmonary surfactant production is influenced by the androgen receptor (AR) (See Nielsen H C. Androgen receptors influence the production of pulmonary surfactant in the testicular feminization mouse fetus. J Clin Invest. 1985; 76(1): 177-181). For example, in rabbits, dihydrotestosterone was shown to inhibit fetal pulmonary surfactant production in both males and females while an anti-androgen, flutamide, was demonstrated to remove the sexual dimorphism in surfactant production.

[0005] While severe COVID-19 symptoms are primarily manifested in older adults, the similar sexual dimorphism in the severity of respiratory disease is of interest. In addition, AR expression is low prior to pubertal maturation and may contribute to the low incidence of severe COVID-19 infection in children. The lower rate of severe COVID-19 infection in female patients may be attributed to lower androgen receptor expression.

SUMMARY

[0006] SARS-CoV-2 is part of the coronavirus family of viruses including SARS-CoV-1 and MERS-CoV. Coronavirus predominantly infects type II pneumocytes in the human lung (See Shieh W J, Hsiao C H, Paddock C D, Guarner J, Goldsmith C S, et al. Immunohistochemical, in situ hybridization, and ultrastructural localization of SARS-associated coronavirus in lung of a fatal case of severe acute respiratory syndrome in Taiwan. Hum Pathol. 2005; 36(3): 303-309). It has been demonstrated that SARS-CoV-2 cell entry depends on priming of a viral spike surface protein by transmembrane protease serine 2 (TMPRSS2) present in the host. In type II pneumocytes, TMPRSS2 expression is associated with an increase in androgen receptor (AR) expression (See Mikkonen L, Pihlajamaa P, Sahu B, Zhang F P, Janne O A. Androgen Receptor and Androgen-Dependent Gene Expression in Lung. Mol Cell Endocrinol. 2010; 317 (1-2): 14-24), specifically connecting AR expression to SARSCoV-2, due to AR-regulated TMPRSS2 gene promoter (See Lin B, Ferguson C, White J T, Wang S, Vessella R, True L D, et al. Prostate-localized and androgen-regulated expression of the membrane-bound serine protease TMPRSS2. Cancer Res 1999; 59: 4180-4). Moreover, angiotensin converting enzyme 2 (ACE2) has been recognized as the attachment